Remarks

Amendments

Claim 2 has been amended to clarify that the reagents for polymerase chain reaction (PCR) used in the claimed method comprise a "pair of primers" in place of "primers." This amendment is consistent with original claim 2 which describes amplification occurring on templates which hybridize to "both primers" (line 11) and that detecting an amplification product indicates the presence of template which hybridizes to "both primers" (line 13). This amendment merely clarifies and does not narrow the scope of claim 2.

Claim 7 has been amended to recite that the primers employed in the method "have sequences as shown in SEQ ID NO: 1 and SEQ ID NO: 2" in place of "are PEU7 and PEU8." The amendment substitutes the sequence identifiers of the referenced primers for their designated names in the application. See the application at page 3, lines 3-5: "The primer pairs are selected from the group consisting of: PEU 7 and PEU 8 (SEQ ID NO 1 and 2), and PEU 4 and PEU 5 (SEQ ID NO: 3 and 4)." This amendment does not narrow the scope of claim 7.

Claim 23 has been amended to recite that the reagents for PCR used in the method comprise a pair of primers "having sequences selected from the group consisting of (a) SEQ ID NO: 1 and 2; and (b) SEQ ID NO: 3 and 4" in place of "from the group consisting of PEU7 and PEU8 (SEQ ID NO: 1 and 2); and PEU4 and 5 (SEQ ID NO:3 and 4)." The amendment merely deletes redundant recitations of the primers employed in the method and does not narrow the scope of the claim. Claim 23 has also been amended to recite that the amplification products detected in the method have "416 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 1 and 2" or "811 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4" in place of have "416 or 811 base pairs." The amendment clarifies which

amplification product is detectable when a particular set of primers is used to amplify template DNA. The specification supports this amendment: "Primers which are particularly suitable in the practice of the present invention are PEU 7 and PEU 8 (SEQ ID NO 1 and 2), and PEU 4 and PEU 5 (SEQ ID NO: 3 and 4). These produce amplification products of 416 or 811 basepairs, respectively." Page 7, lines 25-27. Claim 23 has also been amended to recite that the amplification product indicates the presence "in the patient's blood of a template which hybridizes to both primers of the pair of primers" in place of indicates the presence "of template which hybridizes to both primers in the patient's blood." The amendment merely clarifies claim 23 and does not narrow the scope of claim 23.

None of these amendments introduce new matter.

The Rejection of Claims 2-23 Under 35 U.S.C. § 112, Second Paragraph

Claims 2-23 have been rejected as indefinite on four separate grounds. Each will be discussed in turn.

A. Claim 7 has been rejected as indefinite because the recitation that the primers used in the method are "PEU7 and PEU8" does not clearly describe the primers. Claim 7 has been amended to clarify that the "primers have sequences as shown in SEQ ID NO: 1 and SEQ ID NO: 2."

B. Claim 23 has been rejected as indefinite for the recitation "detecting an amplification product of 416 or 811 base pairs, wherein a detected amplification product indicates the presence of template which hybridizes to both primers in the patient's blood." The Office Action asserts that this recitation is indefinite because it is unclear whether the primers hybridize to the patient's blood or to DNA isolated from the patient's blood. Claim 23 has been amended to recite that the "detected amplification product indicates the presence in the patient's blood of a

template which hybridizes to both primers of the pair of primers." The amendment clarifies that the primers hybridize to a template that is in the patient's blood and not to the patient's blood *per se*.

The Office Action also asserts that this recitation is indefinite because it is unclear which "both primers" of the four primers present in the reagents for PCR hybridize to the template. Claim 23 has been amended to recite that the reagents for PCR comprise primers "having sequences selected from the group consisting of (a) SEQ ID NO: 1 and 2; and (b) SEQ ID NO: 3 and 4." The amendment clarifies that the pair of primers that hybridize to the template is either SEQ ID NO: 1 and 2 or SEQ ID NO: 3 and 4.

The Office Action further asserts that this recitation is indefinite because it is not clear whether the method detects one or two amplification products. Claim 23 has been amended to recite "detecting an amplification product of 416 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 1 and 2, or detecting an amplification product of 811 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4." The amendment clarifies that at least one amplification product is detected in the method, the length of which depends on the whether the primers used for amplification have the sequences of SEQ ID NO: 1 and 2 or the sequences of SEQ ID NO: 3 and 4.

C. The Office Action asserts that the recitation in claims 2-22 that the reagents for PCR include "primers" and that the reagents for PCR are subjected to conditions in which any templates will hybridize to "both primers" is indefinite. The Office Action asserts that this recitation is indefinite because it is unclear which "primers" in the reagents for PCR are the "both primers" that hybridize to template to form an amplification product. Claim 2 has been amended to recite that the reagents for PCR comprise a "pair of primers" and that "both primers

of the pair of primers" hybridize to any templates. The amendment clarifies which primers of the reagents for PCR hybridize to any template.

D. Claim 23 has been rejected as indefinite for reciting "PEU7 and PEU8 (SEQ ID NO: 1 and 2); and PEU 4 and 5 (SEQ ID NO: 3 and 4)." The Office Action asserts that this recitation is indefinite because it is not clear whether the primers are required to comprise sequences of the SEQ ID NO:s, in parentheses. Claim 23 has been amended to recite that the primers have sequences "selected from the group consisting of (a) SEQ ID NO: 1 and 2; and (b) SEQ ID NO: 3 and 4."

Applicant respectfully requests withdrawal of these rejections.

The Rejection of Claims 2, 4-11, 14, 15, and 20 Under 35 U.S.C. § 102(b)

Claims 2, 4-11, 14, 15, and 20 have been rejected under 35 U.S.C. § 102(b) as anticipated by Corless *et al.* (*J. Clin. Microbiol.*, (2000) *38*(5):1747-1748; "Corless"). Applicant respectfully traverses.

Claim 2 is the only independent claim of the rejected claim set. Claim 2 is directed to a method of performing PCR. Reagents for PCR are digested with a restriction endonuclease. The reagents comprise Taq DNA polymerase, deoxynucleotide triphosphates, reaction buffer, and a pair of primers. The restriction endonuclease does not cleave the pair of primers and the pair of primers has no recognition sites for the restriction endonuclease. The restriction endonuclease but not the Taq DNA polymerase is inactivated. The test sample and the reagents for PCR are mixed to form a mixture. The mixture is subjected to conditions such that any templates present in the test sample which hybridize to both primers of the pair of primers are amplified. The amplification product is detected. A detected amplification product indicates the presence of

template which hybridizes to both primers in the test sample.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Corless teaches a method of performing PCR. However, Corless does not teach a "pair of primers [that] has no recognition sites for the restriction endonuclease" as recited in claim 2.

Corless explicitly teaches that the primers used in his PCR method contain recognition sites for the restriction endonuclease. Corless teaches, "Five restriction endonuclease enzymes, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I (Pharmacia Biotech, St. Albans, England) were selected for use in the pretreatment of the PCR master mixture on the basis of the restriction sites identified in the 16S rRNA sequence within the primer binding sites. . ." Page 1748, column 2, lines 27-31. Thus, Corless teaches the use of a pair of primers that includes the recognition sequence of the restriction endonuclease.

The forward primer used in Corless' PCR reagent mixture contains the recognition sequence for several restriction enzymes used to digest his reagents for PCR. Corless teaches that the nucleotide sequence of the forward primer is: 5'-CCATGAAGTCGGAATCG*CTAG*-3'. Page 1748, column 1, lines 47-48. This forward primer contains a *Hin*fI (GANTC, underlined) recognition sequence and a *Sau*3AI (GATC, italicized) recognition sequence. As indicated in the above quotation, *Hin*fI and *Sau*3AI are two of the restriction endonucleases Corless teaches to use to cleave the reagents for PCR. Thus, Corless does not teach a "pair of primers [that] has no recognition sites for the restriction endonuclease" as recited in claim 2. As Corless does not teach this recited element of claim 2, Corless also does not teach this recited element in dependent claims 4-11, 14, 15, and 20. Applicant respectfully requests withdrawal of this

rejection.

The Rejection of Claims 2-4, 8-10, and 18 Under 35 U.S.C. § 102(b)

Claims 2-4, 8-10, and 18 have been rejected under 35 U.S.C. § 102(b) as anticipated by DeFilippes (*Biotechniques* (1991) *10*(1):26-30). Applicant respectfully traverses.

Claim 2 is the only independent claim of the rejected claim set. As indicated above, claim 2 includes a step of digesting reagents for PCR with a restriction endonuclease. The "reagents comprise Taq DNA polymerase, deoxynucleotide triphosphates, reaction buffer, and a pair of primers."

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

DeFilippes teaches a method of performing PCR. DeFilippes, however, does not teach "digesting reagents for polymerase chain reaction with a restriction endonuclease wherein the reagents comprise Taq DNA polymerase" as recited in claim 2.

DeFilippes teaches digesting reagents for PCR that include only the pair of primers, deoxyribonucleotides, and template DNA. DeFilippes teaches, "Thirty-microliter RE digestion reaction contained 0.1 nmol of each priming deoxyoligonucleotide that would be used in the ensuing PCR, 20 nmol of each deoxyribonucleotide (for the PCR), template DNA, RE buffer and RE(s)." Page 28, column 1, lines 24-30. DeFilippes teaches that Taq DNA polymerase is added to the reagents for PCR after restriction endonuclease digestion is complete and the restriction endonuclease has been inactivated. "After the REs were inactivated by heating at 90°C for 20 min, 10 μl of modified 10x PCR buffer (500 mM KCl, 100 mM Tris-Cl, pH 8.3) and 1.25 units

of *Taq* polymerase (AmpliTaq® DNA Polymerase, Perkin-Elmer Cetus, Norwalk, CT) were added to the digest and the volume was increased to 100 µl." Page 28, column 1, lines 31-39. Thus, DeFilippes does not teach digesting reagents that include Taq DNA polymerase with a restriction endonuclease, inactivating the restriction endonuclease. Since digesting reagents for PCR with a restriction endonuclease "wherein the reagents comprise Taq DNA polymerase" is an element recited in claim 2, DeFilippes does not teach each and every element recited in claim 2 or dependent claims 3, 4, 8-10, and 18. Applicant respectfully requests withdrawal of this rejection.

The Rejection of Claims 13, 17, 19, 21, and 22 Under 35 U.S.C. § 103(a)

Claims 13, 17, 19, 21, and 22 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Corless in view of Lu *et al.* (*J. Clin. Microbiol.* (2000) *38*(5):1747-1748; "Lu"). Applicant respectfully traverses.

Claims 13, 17, 19, 21, and 22 all depend from claim 2. Claim 2, discussed above, is directed to a method of performing polymerase chain reaction that includes a step of digesting reagents for PCR with a restriction endonuclease. Claim 13 specifies that the test sample mixed with the reagents for PCR is cerebral spinal fluid. Claim 17 recites that the method of claim 2 further comprises a step of identifying a bacterial species as a source of the templates by restriction endonuclease digestion of the amplification product and determining sizes of products of the digestion. Claim 19 recites that the Taq DNA polymerase is not active under the conditions used to the step of digesting. Claims 21 and 22 specify that the amplified product contains at least one or two recognitions sites for the restriction endonuclease, respectively. Lu is cited as teaching the added recitations in each of these dependent claims.

To reject claims as *prima facie* obvious the Patent Office must meet three criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143.

The Patent Office has failed to make a *prima facie* case of obviousness of claims 13, 17, 19, 21, and 22 because one of ordinary skill in the art would not have combined Corless and Lu to arrive at the claimed invention, *i.e.*, the Patent Office has failed to meet the first criterion.

When determining the patentability of a claimed invention which combines two known elements, there must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *In re Beattie*, 974 F.2d 1309 (Fed. Cir. 1992) (quoting *Lindemann*, 730 F.2d at 1462, (Fed. Cir. 1984)). As a prior art reference must be considered in its entirety, even portions that would lead away from the claimed invention must be considered. When there is such a clear teaching away in the prior art, the prior art would not suggest the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Independent claim 2, from which claims 13, 17, 19, 21, and 22 depend, recites that the method of performing polymerase chain reaction employs a "pair of primers [that] has no recognition sites for the restriction endonuclease." As discussed above, Corless does not teach the use of a pair of primers that has no recognition sites for the restriction endonuclease. Corless specifically teaches that the primers used in his PCR method should have recognition sites for the restriction endonucleases. Corless teaches, "Five restriction endonuclease enzymes, *Ava*I,

*Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I (Pharmacia Biotech, St. Albans, England) were selected for use in the pretreatment of the PCR master mixture on the basis of the restriction sites identified in the 16S rRNA sequence within the primer binding sites. . ." Page 1748, column 2, lines 27-31. Thus, Corless does not teach a PCR method that uses a "pair of primers [that] has no recognition sites for the restriction endonuclease" as recited in the rejected claims. Corless also does not suggest such a pair of primers.

Lu teaches a PCR method for detecting a bacterial pathogen in a sample. The Lu PCR method includes steps of amplifying a portion of the 16S rRNA gene of eubacteria with a set of primers, obtaining an amplification product, digesting the amplification product with a restriction enzyme to produce digestion products, and detecting the digestion products to determine which species of eubacteria is present in the sample. Page 2079, column 1, lines 1-11 of the Discussion. The primers of Lu method were designed to be capable of amplifying rRNA from a maximum number of species of bacteria. Lu teaches the following about the sequence of the primers used in the method: "The sequence of primer U1 is 5'-CCAGCAGCCGCGGTAATACG-3', corresponding to nucleotides 518 to 537 of the E. coli 16S rRNA gene, and that of U2 is 5'-ATCGG(C/T)TACCTTGTTACGACTTC-3', corresponding to nucleotides 1513 to 1491 of the same gene." Page 2077, sentence bridging columns 1 and 2. Neither of these primers has a recognition sequence for any of the restriction endonucleases taught by Corless, *i.e.*, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I.

One of ordinary skill in the art would not have been motivated to modify Corless' method of performing PCR by using Lu's pair of primers because Corless explicitly teaches away from using such a pair of primers. Corless teaches, "Five restriction endonuclease enzymes, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I (Pharmacia Biotech, St. Albans, England) were selected for use

in the pretreatment of the PCR master mixture on the basis of the restriction sites identified in the 16S rRNA sequence within the primer binding sites. . ." Page 1748, column 2, lines 27-31. Because Corless specifically teaches away from the use of the pair of primers taught by Lu, one of ordinary skill in the art would not have been motivated to incorporate Lu's primers into Corless' PCR method. Thus one of ordinary skill in the art would not have been motivated to combine Corless and Lu to arrive at the claimed invention and a *prima facie* case of obvious of claims 13, 17, 19, 21, and 22 must fail.

Applicant respectfully requests withdrawal of this rejection.

The Rejection of Claims 12, 13, 17, and 19 Under 35 U.S.C. § 103(a)

Claims 12, 13, 17, and 19 are rejected under 35 U.S.C. § 103(a) as unpatentable over Corless in view of Mariani *et al.* (U.S. Patent No. 5,654,141; "Mariani"). Applicant respectfully traverses.

Claims 12, 13, 17, and 19 all depend from claim 2. Claim 2, discussed above, is directed to a method of performing PCR. Claims 12 and 13 further recite that the sample mixed with the reagents for PCR is urine and cerebral spinal fluid, respectively. Claim 17 recites further a step of identifying a bacterial species as a source of the templates by restriction endonuclease digestion of the amplification product and determining sizes of products of the digestion. Claim 19 further recites that the Taq DNA polymerase is not active under the conditions used to the step of digesting. Mariani is cited as teaching the recitations of each of these dependent claims.

When determining the patentability of a claimed invention which combines two known elements, there must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *In re Beattie*, 974 F.2d 1309 (Fed. Cir. 1992)

(quoting *Lindemann*, 730 F.2d at 1462, (Fed. Cir. 1984)). As a prior art reference must be considered in its entirety, even portions that would lead away from the claimed invention must be considered. When there is such a clear teaching away in the prior art, the prior art would not suggest the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Independent claim 2, from which claims 12, 13, 17, and 19 depend, recites a step of digesting reagents for PCR with a restriction endonuclease. The reagents for PCR include a "pair of primers [that] has no recognition sites for the restriction endonuclease." As discussed above, Corless does not teach a pair of primers that has no recognition sites for the restriction endonuclease. Corless specifically teaches that the primers used in his PCR method have the restriction enzyme recognition sequences. Page 1748, column 2, lines 27-31.

Mariani teaches a PCR method for detecting a bacterial infection. Mariani teaches that the PCR method includes steps of "obtaining a patient sample; obtaining a sample of nucleic acids from the patient sample; amplifying the nucleic acids; and detecting the presence or absence of amplified nucleic acids specific for a bacterial infection wherein the presence of amplified nucleic acids indicates a bacterial infection." Column 1, line 67 to column 2, line 5. Mariani teaches that the primers used in his method include any of his SEQ ID NOs: 1-7:

> Sequences useful in the amplification methods of the present invention include and are not limited to SEQ ID NO: 1, targeted to the 5' half of the 16S rRNA gene, CGGCAGGCCTAACACATGCAAGTCG and SEQ ID NO: 2, targeted to the 3' half of the 16S rRNA gene, GGTTGCGGCCGTACTCCCCAGG. SEQ ID NOS: 1 and 2 are sequences of 16S rRNA gene which are conserved among Escherichia, Streptococcus, Staphylococcus, Bacteroides, and the like. The primers sequences of the present invention were originally isolated from E. coli. Non-conserved sequences of the 16S rRNA gene may also be used in the present invention to

> identify Escherichia, Streptococcus, Staphylococcus, or Bacteroides. The following sequences may be used in regard to the ial gene of E. coli, the 5' sequence TAATACTCCTGAACGGCG (SEQ ID NO: 3) and the 3' sequence TTAGGTGTCGGCTTTTCTG (SEQ ID NO: 4), Enterotoxin A gene of Staphylococcus, including aureus and S. epidermidis, TTGGAAACGGTTAAAACGAA (SEQ ID NO: 5) and GAACCTTCCCATCAAAAACA (SEQ ID NO: 6), the 16S non-conserved region of Bacteroides fragilis, GACGTAAGGGCCGTGCTGATTTGACGTC, (SEQ ID NO: 7) used with universal 16S primer; and various primers that target the non-conserved region of other non-conserved 16S regions depending on species such as species of Streptococcus.

Column 4, lines 31-55. Mariani's SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6 are each primers that do not have a recognition site for any of the restriction endonucleases taught by Corless for performing PCR, *i.e.*, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I.

One of ordinary skill in the art would not have been motivated to modify Corless to employ any of Mariani's primers because Corless explicitly teaches that restriction endonuclease recognition sites are desirable. Corless teaches, "Five restriction endonuclease enzymes, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I (Pharmacia Biotech, St. Albans, England) were selected for use in the pretreatment of the PCR master mixture on the basis of the restriction sites identified in the 16S rRNA sequence within the primer binding sites. . ." Page 1748, column 2, lines 27-31. Because Corless specifically teaches away from the use of the pair of primers taught by Mariani, one of ordinary skill in the art would not have been motivated to incorporate Mariani's primers into Corless' PCR method. Thus one of ordinary skill in the art would not have combined Corless and Mariani to arrive at the claimed invention and a *prima facie* case of obvious of 12, 13, 17, and 19 must fail.

Applicant respectfully requests withdrawal of this rejection.

The Rejection of Claim 16 Under 35 U.S.C. § 103(a)

Claim 16 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Corless in view of Dodge *et al.* (U.S. Patent No. 6,054,278; "Dodge"). Applicant respectfully traverses.

Claim 16 depends from claim 2. Claim 2, discussed above, is directed to a method of performing polymerase chain reaction. Claim 16 further recites that the step of identifying a bacterial species as a source of the templates by sequencing the amplification product. Dodge is cited as teaching this recitation of claim 16.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Independent claim 2, from which claim 16 depends, recites a method of performing polymerase chain reaction that includes a step of digesting reagents for PCR with a restriction endonuclease. The reagents for PCR include a "pair of primers [that] has no recognition sites for the restriction endonuclease." As discussed above, Corless does not teach a pair of primers that have no recognition sites for the restriction endonuclease. Corless specifically teaches that the primers used in his PCR method have the restriction enzyme recognition sequences. Page 1748, column 2, lines 27-31.

Dodge also fails to teach such a pair of primers and thus fails to remedy the deficiency of Corless. Dodge teaches a method of generating composite nucleotide sequences[1] of bacterial

[1] "The term 'composite polynucleotide sequence' refers to polynucleotide sequence information that is generated by confining at least two constituent polynucleotide sequences into a single polynucleotide sequence representative of the constituent polynucleotides so as to indicate the nucleotides bases that are in common between the constituent sequences and the nucleotide bases that vary, i.e., are polymorphic, between the constituent sequences." Column 3,

16S rRNA genes. Dodge teaches that the method includes steps of purifying polynucleotides from a microorganism of interest, amplifying all or a portion of the 16S rRNA gene, and sequencing the amplified all or a portion of the 16S rRNA gene. Column 5, lines 11-16. Analysis of the sequence information obtained from the 16S rRNA genes produces the composite sequence. Column 6, lines 14-18. Dodge teaches that her PCR primers are designed to anneal to nucleic acids flanking all or a portion of the 16S rRNA gene. Dodge teaches "PCR, and related polynucleotide amplification techniques employ pairs of primers that bracket the sequence to be amplified. Preferably, the amplification primers are designed to amplify the entire or substantially the entire 16S rRNA gene." Column 6, lines 40-44. Dodge does not teach or suggest that the method includes a step of digesting the PCR reagents with a restriction endonuclease and thus does not teach or suggest using a "pair of primers [that] has no recognition sites for the restriction endonuclease." As neither Corless nor Dodge teaches "a "pair of primers [that] has no recognition sites for the restriction endonuclease" the combination of Corless and Dodge fails to teach or suggest all the elements recited in claim 16. The *prima facie* case of obviousness must fail.

Applicant respectfully requests withdrawal of this rejection.

The Rejection of Claim 23 Under 35 U.S.C. § 103(a)

Claim 23 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Corless in view of Dodge, Everett *et al.* (U.S. Patent No. 6,261,769; "Everett"), and Dunbar *et al.* (*Appl. Environ. Microbiol.*, (1999) *65*(4):1662-1669; "Dunbar"). Applicant respectfully traverses.

Claim 23 is directed to a method of performing PCR. Reagents for PCR are digested

---

lines 15-22.

with *Alu*I restriction endonuclease. The reagents comprise *Taq* DNA polymerase, deoxynucleotide triphosphates, reaction buffer, and a pair of primers having sequences selected from the group consisting of (a) SEQ ID NO: 1 and 2; and (b) SEQ ID NO: 3 and 4. The *Alu*I restriction endonuclease is inactivated by heating the reagents to a temperature which inactivates *Alu*I but does not inactivate *Taq* DNA polymerase. A test sample of DNA isolated from a patient's blood sample is mixed with the reagents for PCR to form a mixture. The mixture is subjected to conditions such that any template present in the test sample which hybridizes to both primers is amplified. If the patient has bacteremia, an amplification product of 416 basepairs or 811 basepairs is detected.

To reject claims as *prima facie* obvious the Patent Office must meet three criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143. The Patent Office has failed to make a *prima facie* case of obviousness of claim 23 because the rejection fails to meet the third criterion, *i.e.*, Corless, Dodge, Everett, and Dunbar fail to teach or suggest all the elements recited in claim 23.

Corless teaches a general method of performing PCR. Corless is cited as teaching digesting reagents for PCR with restriction endonucleases, inactivating the restriction endonuclease but not Taq DNA polymerase, mixing test sample with the reagents for PCR, subjecting the mixture to conditions such that any templates present in the test sample which hybridize to both primers are amplified, and detecting an amplification product. Corless does not, however, teach or suggest two elements recited in claim 23. Corless does not teach or

suggest: (1) "digesting reagents for polymerase chain reaction with AluI restriction endonuclease" and (2) "detecting an amplification product of 416 base pairs if the selected pair of primers has the sequences of SEQ ID NO: 1 and 2 or detecting an amplification product of 811 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4." None of Dodge, Everett and Dunbar remedies these deficiencies.

digesting reagents for polymerase chain reaction with *Alu*I

Corless does not teach cleavage of reagents for PCR with *Alu*I as recited in claim 23. Corless teaches, "Five restriction endonuclease enzymes, *Ava*I, *Hae*III, *Hin*fI, *Sau*3AI, and *Sma*I (Pharmacia Biotech, St. Albans, England) were selected for use in the pretreatment of the PCR master mixture on the basis of the restriction sites identified in the 16S rRNA sequence within the primer binding sites. . ." Page 1748, column 2, lines 27-31. Corless does not teach employing *Alu*I as the restriction endonuclease to cleave reagents for PCR. Corless also does not suggest varying the restriction endonucleases that he taught.

Dodge also does not teach or suggest "digesting reagents for polymerase chain reaction with AluI restriction endonuclease" as recited in claim 23 and thus fails to remedy this deficiency of Corless. Dodge teaches a method of generating composite nucleotide sequences of bacterial 16S rRNA genes. Dodge teaches that the method includes steps of purifying polynucleotides from a microorganism of interest, amplifying all or a portion of the 16S rRNA gene, and sequencing the amplified all or a portion of the 16S rRNA gene. Column 5, lines 11-16. Dodge does not teach or suggest digesting PCR reagents with a restriction endonuclease and thus does not teach or suggest "digesting reagents for polymerase chain reaction with AluI restriction endonuclease."

Everett also fails to remedy this deficiency of Corless. Everett teaches the nucleotide

sequences of regions of the genome of Chlamydiaceae, including an intergenic spacer between the 16S and 23S rRNA genes and the 3' end of a portion of the 23S gene. Everett teaches that within these two regions are nucleotide sequences that can be used in assays to detect Chlamydiaceae. These assays include steps of amplifying a portion of a Chlamydiaceae genome and detecting amplified product. Column 9, lines 53-67. See also column 10, lines 25-65. Everett does not teach or suggest digesting the PCR reagents with a restriction endonuclease and thus does not teach or suggest "digesting reagents for polymerase chain reaction with AluI restriction endonuclease."

Dunbar also does not teach or suggest "digesting reagents for polymerase chain reaction with AluI restriction endonuclease" as recited in claim 23 and thus fails to remedy this deficiency of Corless. Dunbar teaches analysis of bacterial phylotypes. Dunbar teaches determining bacterial phylotypes by culturing bacteria samples (page 1663, column 1, lines 52-61), directly subjecting the bacterial cultures to amplification (page 1663, column 1, lines 62-71), and either digesting the resulting amplification products (page 1663, column 1, lines 73-78) or purifying and sequencing the resulting amplification products (page 1664, column 2, lines 11-23). Dunbar does not teach or suggest that the method includes a step of digesting the PCR reagents with a restriction endonuclease and thus does not teach or suggest "digesting reagents for polymerase chain reaction with AluI restriction endonuclease."

None of Corless, Dodge, Everitt, and Dunbar teaches or suggests "digesting reagents for polymerase chain reaction with AluI restriction endonuclease" as recited in claim 23. As the combination of Corless, Dodge, Everitt, and Dunbar fails to teach or suggest all the elements recited in claim 23, the *prima facie* case of obviousness must fail.

detecting an amplification product of 416 base pairs if the pair of primers has the sequences of SEQ ID NO: 1 and 2

Corless does not teach or suggest employing a primer in his method of performing PCR that has the sequence of any one of SEQ ID NOs: 1-4. The Office Action acknowledges that Corless does not teach any of these primers: "Corless et al. did not teach PCR primers selected from the group consisting of SEQ ID Nos. 1-4." Office Action at page 14, lines 3-4. Corless also does not suggest modifying the primers taught and thus does not suggest a primer having the sequence of any of SEQ ID NOs: 1-4. The Office Action cites Dodge, Everitt, and Dunbar as teaching SEQ ID NO: 1-4.

Dodge is cited as teaching the nucleotide sequence of applicant's SEQ ID NO: 1. Dodge teaches a sequencing primer (primer 0776F; SEQ ID NO: 9, see column 10, line 61) that contains the sequence of applicant's SEQ ID NO: 1. Applicant's SEQ ID NO: 1 corresponds to nucleotides 2-21 of Dodge's 24 nucleotide sequencing primer. See alignment provided with Office Action. Thus, Dodge teaches a primer having the sequence of Applicant's SEQ ID NO:1 within a larger sequence.

Everitt is cited as teaching a nucleotide sequence that contains recited SEQ ID NO: 2. Everitt teaches the nucleotide sequence of several Chlamydiaceae genomes at the region encoding the 16S rRNA and 23S rRNA genes. Everitt teaches a nucleotide sequence (SEQ ID NO: 6) that is a 2751 nucleotide genomic sequence of *Chlamydia psittaci* encoding the 16S rRNA gene, 23S rRNA gene, and the intergenic spacer between the 16S and 23S rRNA genes. Applicant's SEQ ID NO: 2 corresponds to nucleotides 193-212 of Everitt's 2751 nucleotide sequence. See alignment provided with the Office Action. Thus Everitt teaches a 2751 nucleotide sequence having the sequence of SEQ ID NO: 2 within a larger sequence.

The Office Action does not indicate that Dunbar teaches or suggests a sequence containing SEQ ID NO: 1 or SEQ ID NO: 2. Thus, Applicant does not believe that Dubar teaches or suggests either of these sequences.

The combination of Corless, Dodge, Everitt, and Dunbar does not teach or suggest claim 23's recitation of "detecting an amplification product of 416 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 1 and 2." Modification of Corless' PCR method to use Dodge's 24-nucleotide sequencing primer and Everitt's 2751 nucleotide *Chlamydia psittaci* genomic sequence would not produce an amplification product of 416 basepairs as required in claim 23. Amplification with Dodge's 24-nucleotide primer and Everitt's 2751-nucleotide molecule will generate a product of at least 2775 base pairs (24 + 2751 nucleotides, *i.e.*, the size of the two proposed primers). Thus, the combination of Corless, Dodge, and Everitt, does not teach or suggest "detecting an amplification product of 416 base pairs if the selected pair of primers has the sequences of SEQ ID NO: 1 and 2."

<u>detecting an amplification product of 811 basepairs if the pair of primers has the sequences of SEQ ID NO: 3 and 4</u>

As indicated above, Corless does not teach or suggest any of SEQ ID NOs: 1-4. The Office Action acknowledges that Corless does not teach any of these primers: "Corless et al. did not teach PCR primers selected from the group consisting of SEQ ID Nos. 1-4." Office Action at page 14, lines 3-4.

Dodge is not cited in the Office Action as teaching a sequence containing SEQ ID NO: 3 or SEQ ID NO: 4. Thus, applicant believes that Dodge does not teach or suggest either of these sequences.

Everitt is cited as teaching a nucleotide sequence containing the sequence of recited SEQ

ID NO: 3. Everitt teaches a nucleotide sequence at SEQ ID NO: 26 that contains the nucleotide sequence of recited SEQ ID NO: 3 within a larger sequence. Everitt's SEQ ID NO: 26 is a 1284 nucleotide genomic sequence of *Chlamydia pneumoniae* encoding the 16S rRNA gene, 23S rRNA gene, and the intergenic spacer between the 16S and 23S rRNA genes. The applicant's SEQ ID NO: 3 corresponds to nucleotides 67-46 of this 1284 nucleotide sequence. See alignment provided with the Office Action.

Dunbar is cited as teaching a nucleotide sequence containing the sequence of recited SEQ ID NO: 4 within it. Dunbar teaches a nucleotide sequence of the 16S rRNA gene of a bacterial phylotype. The sequence was deposited in GenBank as accession number AF128731. Accession number AF128731 is a 410 nucleotide sequence that contains the sequence of SEQ ID NO: 4 at nucleotides 171-191. See alignment provided with the Office Action.

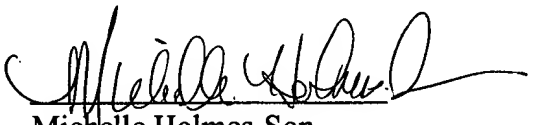
The combination of Corless, Dodge, Everitt, and Dunbar does not teach or suggest "detecting an amplification product of 811 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4." Modification of Corless' PCR method to use Everitt's 1284-nucleotide *Chlamydia pneumoiae* genomic sequence, which contains Applicant's SEQ ID NO:3, and Dunbar's 410-nucleotide 16S rRNA gene, which contains SEQ ID NO: 4, would not produce an amplification product of 811 basepairs as required in claim 23. Amplification with Everitt's 1284- and Dunbar's 410-nucleotide molecule would generate a product at least 1694 base pairs (1284 + 410 nucleotides, *i.e.*, the size of the two primers). Thus, the combination of Corless, Dodge, and Everitt, does not teach or suggest "detecting an amplification product of 811 base pairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4."

The combination of Corless, Dodge, Everitt, and Dunbar simply does not teach or suggest "detecting an amplification product of 416 base pairs if the selected pair of primers has the

sequences of SEQ ID NO: 1 and 2 or detecting an amplification product of 811 basepairs if the selected pair of primers has the sequences of SEQ ID NO: 3 and 4" as recited in claim 23. Thus, the combination of these references fails to teach or suggest all the elements recited in claim 23 and the prima facie case of obviousness must fail.

Applicant respectfully requests withdrawal of this rejection.

Respectfully submitted,

By: 

Michelle Holmes-Son
Registration No. 47,660

Date: November 23, 2004

Customer No. 22907